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Calm !

VASOTEC®

(ENALAPRIL MALEATE | MSD)

VASOTEC is available in 2.5-mg, 5-mg, 10-mg, and 20-mg tablet strengths.

Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings: *Angioedema:* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Patients with heart failure given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions.*)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Pregnancy–Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies of enalapril in pregnant women. However, data are available that show enalapril crosses the human placenta. Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined, VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

HYPERTENSION: The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

HEART FAILURE: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances; atrial fibrillation; palpitation.

Digestive: Ileus, pancreatitis, hepatitis (hepatocellular or cholestatic jaundice), melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth.

Musculoskeletal: Muscle cramps.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Respiratory: Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection.

Skin: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, hyperhidrosis.

Special Senses: Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgias/arthritis, myalgias, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash, and other dermatologic manifestations.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings:

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported. A few cases of hemolysis have been reported in patients with G6PD deficiency.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: *Hypertension:* In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects.*) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia: In patients with heart failure who have hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine >1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, *Heart Failure*, WARNINGS, and PRECAUTIONS, *Drug Interactions.*) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD Representative or see Prescribing Information, Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, PA 19486. J9VS50R4(819)